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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,763	05/20/2005	Stefan Werner	049202/289226	9269

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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,763	WERNER ET AL.	
	Examiner	Art Unit	
	BRENT PAGE	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,11-14,17,18,23,25-27 and 29-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,11-14,17,18,23,25-27 and 29-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 and 11-14, 17-18, 23, 25-27 and 29-31 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Klimyuk et al (WO02088369) in view of Hooykaas et al (WO0189283) and further, in view of Xu et al (WO 0071701).

The claims are broadly drawn to multicellular organisms and methods of controlling multicellular organisms comprising providing any genetically modified organism or cell containing any heterologous nucleic acid and causing expression of a polypeptide into cells of said genetically modified plant, wherein the plant or cells contain an additional heterologous nucleic acid that controls a cellular process of interest, wherein said nucleic acid encoding protein causes the formation of an RNA and/or protein expression product, or an expressible amplicon, wherein the heterologous nucleic acid is stably integrated in the nuclear genome of said organism.

Klimyuk et al (WO02088369, published 11/07/2002) teach a method for expressing a nucleic acid sequence of interest in plants providing at least two precursor vectors (claim 2 and meets the limitation of additional heterologous nucleic acid) wherein the processing of the precursor is by RNA splicing, ligation

and recombination (claim 13), wherein the cell provides in trans functions necessary for replicon replication, virus particle assembly (claim 18), wherein the genetic engineering is done by virus or Agrobacterium mediated transfection wherein the process results in the expression of multiple genes of a biochemical pathway or cascade (claims 19 and 21 and 23) wherein the heterologous sequence is integrated stably into a host chromosome (claim 27), and wherein the heterologous nucleic acid introduced is a vector comprising TMV, a viral movement protein and the introduction of CRE into the cell, when jointly present with the LOX sites, commences RNA production from the amplicon (see Examples).

Klimyuk et al do not teach the intein-based trans-splicing or the introduction of a polypeptide into the cell.

Hooykaas et al (WO0189283 published 05/21/2001) teach the translocation of the CRE polypeptide into plant cells using VirE2 and trans-splicing to achieve recombination to induce the transcription of a heterologous gene, NPTII, (See claims and Examples).

Xu et al (WO0071701 published 05/23/2000) teach the use of the intein-mediated system for trans-splicing a first polypeptide fragment with a second polypeptide to achieve gene function.

Given the state of the art and the disclosures by Klimyuk et al, Hooykaas et al and Xu et al, it would have been obvious to one of ordinary skill in the art to modify the method taught by Klimyuk et al by using the system taught by Klimyuk et al to translocate recombinase into the cell as taught by Hooykaas et al and

suggested by Klimyuk et al when stating "A serious concern with prior art virus-based plant expression systems is biological safety" expressing a long felt need to improve the safety of plant expression systems.

Several elements of the claims are well-known in the art and considered to be design choices. The intein trans-splicing method was known in the art at the time of invention, as was the VirE2 system of translocating polypeptides into plant cells. Further it is noted that the limitation of the claims only requires the second polypeptide to comprise “a” fragment of the first protein, and thus, an unspecified fragment may comprise any number of amino acids.

Response to Arguments

Applicant's arguments filed 03/16/2010 have been fully considered but they are not persuasive.

Applicants urge that the Examiner seems to have disregarded most of Applicants’ arguments in the previous response (see page 6 of response).

This is not persuasive because the arguments related to the primary argument that one of ordinary skill in the art would not have combined the references, the argument of which was addressed in the office action mailed out 09/16/2009. Furthermore, Applicants addressed the references individually rather than as a whole. Nonetheless, since many of the arguments are stated in the current response, they will be answered herein below.

Applicants urge that their invention differs from Hooykaas et al in that a plant organism is provided and a step of causing expression by delivering a polypeptide wherein the heterologous DNA is the target of the recombinase or

integrase delivered “as well as for the protein expressed from the nucleic acid”, wherein Hooykaas et al provide a plant with a heterologous nucleic acid that is the target for CRE recombinase delivered as a fusion with part of the VirE by the transfer system of Hooykass et al. (see page 7 of response).

This is not persuasive because Applicant’s own statements put the teachings of Hooykaas within the claim limitations as the claims are currently written. Applicants appear to be misconstruing the statements made by the Examiner to mean that the Examiner believes the CRE recombinase delivered by Hooykaas is equated to the heterologous DNA provided in the plant of the current invention. It should be clear that Applicants have been urging that the difference between the heterologous DNA of the instant invention and Hooykaas is patentably distinct and that the difference is that Applicants’ encoded protein is in itself a fusion protein and recombinase. To state it more clearly the Examiner's position, Applicants teach introducing a polypeptide into a plant with a heterologous nucleic acid that is a target for recombinase or integrase. Hooykaas et al also teach introducing a polypeptide into a plant with a heterologous nucleic acid that is a target for recombinase. In Hooykaas’ system, the introduced polypeptide is capable of cell to cell movement and controls the plant process. In Applicants’ system, the heterologous DNA encodes this particular polypeptide. While Applicant urges that this provides an extra step that Hooykaas et al do not teach (see page 7, paragraphs 3-4 of response), the Examiner’s position is that the same control process is used by both systems, and that Hooykaas does not limit what heterologous proteins could be encoded

in the disclosed system and further, state "The fusion protein to be transferred can either be formed in the transfer system itself, for example, by expressing a vector containing a functional gene system that may be expressed yielding the fusion protein, or the fusion protein itself may be introduced into the transport system" (see paragraphs 12-20 of disclosure), clearly suggesting the combination that would result in the instant invention.

Applicants urge that Hooykaas et al contains no suggestion of nucleic acid being capable of causing its own expression from the heterologous nucleic acid (see page 7, paragraph 5).

This is not persuasive because the instant claims do not recite a limitation that requires a protein, polypeptide or nucleic acid that is capable of causing its own expression. Additionally, it is noted that even if the claims did recite such a limitation, that any polypeptide capable of switching on a heterologous transcript would inherently be "capable" of causing it's own expression, and that this limitation still does not require it to cause it's own expression. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e.,capable of causing it's own expression) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants further urge that "Hooykaas *et al*. does not suggest to use a nucleic acid encoding the recombinase, wherein the nucleic acid is the target for

the recombination activity of the recombinase" (see paragraph 1 of page 8 of the response.

This is not persuasive because firstly, as noted above, the claims do not harbor such limitations, particularly since the claims do not state the introduced polypeptide must be the same polypeptide as the protein encoded by the heterologous DNA, and secondly, can not be inferred since the claims themselves do not specify which polypeptide is introduced, nor which protein is expressed beyond a broad scope of any site-specific recombinase or integrase.

It is furthermore suggested that if Applicant intends the Examiner to examine the claims based on this interpretation that the claims be amended to reflect the narrower scope upon which Applicants are urging in their response. New Matter should be avoided.

Applicants urge that "such a construction..." (referring to the suggestion to use a nucleic acid encoding the recombinase) "…would require the delivery of the fusion protein into cells as a nucleic acid, which is in contradiction with the very teaching of Hooykaas *et al*., which intends to translocate polypeptides, as opposed to nucleic acids, into cells" (see paragraph 2 of page 8 of the response).

This is not persuasive because firstly Hooykaas et al, suggests such a combination as discussed above, and secondly, because Applicants have not demonstrated why one of ordinary skill in the art would not have made that combination as suggested by Hooykaas et al.

Applicants urge that Hooykaas et al do not disclose cells containing a heterologous nucleic acid encoding a protein comprising a protein portion

enabling leaving a cell and entering other cells and a segment selected from the group consisting of a site-specific recombinase and an integrase (see paragraphs 4-6 on page 8 of the response).

This is not persuasive because Hooykaas et al teach a protein comprising a protein portion enabling leaving a cell and entering other cells and a segment selected from the group consisting of a site-specific recombinase and an integrase as discussed above, and further, teach "The fusion protein to be transferred can either be formed in the transfer system itself, for example, by expressing a vector containing a functional gene system that may be expressed yielding the fusion protein, or the fusion protein itself may be introduced into the transport system" (see paragraphs 12-20 of disclosure). Furthermore, it is noted that Applicants are primarily urging against a single reference, without the context of the other references of the 103. Hooykaas teaches two critical features of the instant claims, namely the fusion protein of the instant claims, as well as the direct introduction of a polypeptide to switch on a heterologous nucleic acid. Hooykaas et al fully recognize that various methods could be used to employ the fusion protein including as a heterolous DNA. Klimyuk et al and Xu et al demonstrate the state of the art particularly involving methods of genetic control using precursor vectors and wherein a gene may switch on the expression of such a heterologous nucleic acid. Finally, in response to Hooykaas not disclosing a heterologous nucleic acid encoding a protein "capable of causing expression of said protein (item (ii) of claim 1), *i.e.*, its own expression, once again, Applicants attention is drawn to the fact that the current claims as

written do not contain such a limitation. Even if the claims did contain such a limitation, Applicants have not explained why Hooykaas' suggestions to use the taught fusion protein as a heterologous DNA construct does not provide motivation to both introduce it and use it as a heterologous nucleic acid which meets even the urged limitations of Applicants invention.

Applicants urge that Klimyuk et al does not disclose a link between Hooykaas et al and claims 1 and 27 and do not teach a fusion protein that causes its own expression (see 1st paragraph on page 9 of response).

This is not persuasive because as noted above, such a limitation is not part of the current claims. Furthermore this is not persuasive because Hooykaas et al already teaches such a fusion protein. There is no need to rely on Klimyuk for elements that are already disclosed by Hooykaas et al. Rather, Klimyuk et al establish that the elements of the claimed invention, at least separately, were known and used in the prior art for the aim of controlling processes in a plant as in the instant invention. Using the fusion protein of Hooykaas et al in such a system results in the instant invention.

Applicants urge that neither Klimyuk et al nor Hooykaas et al disclose a protein capable of causing its own expression (see page 9 of response).

This is not persuasive because as discussed above, the term “capable” would apply to any protein that may be used to turn on a gene, whether it is a recombinase or polymerase or any other type of protein switch. It is further not persuasive because this limitation is not present in the claims as currently written.

No claims are free of the prior art.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRENT PAGE whose telephone number is (571)272-5914. The examiner can normally be reached on Monday-Friday 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571)-272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brent T Page

/Anne Marie Grunberg/

Supervisory Patent Examiner, Art Unit 1638